Iron Regulation

Introduction

Red blood cells carry oxygen via hemoglobin. Hemoglobin is made from heme and globin. Heme is made from porphyrin and iron. Because the bone marrow is always dividing, is always making new red blood cells, new hemoglobin must always be synthesized. This lesson focuses on the physiology of iron metabolism. It is complex, is regulated across multiple organs, and has only recently been well elucidated.

We will be discussing several molecules, each of them containing, in one way or another, the word "iron." If it is your first time seeing them, it will be easy to confuse them. Iron (Fe) is the element. **Transferrin** is the transport for iron through the bloodstream. **Ferritin** is the stored form of iron. **Ferroportin** is an iron transporter in enterocytes. Likewise, there are two H-words that sound similar (and don't have "ferr" in their names). **Hemosiderin** is the waste form of iron in cells. Most cells do not like iron. Presence of hemosiderin is generally considered a pathologic state. And **hepcidin** is the regulatory molecule of iron metabolism that comes from the liver. As we proceed, we will reintroduce these molecules as we encounter them.

How Iron Gets into the Body

Iron is absorbed by the enterocytes of the **duodenum only**. There, apical transporters (divalent metal cotransporter 1, or **DMT1**) act as cotransporters to bring iron and H^+ ions into the cell. Iron can exist as Fe^{3+}, which is not readily absorbed by the divalent cotransporter, and as Fe^{2+}, which is readily absorbed by the divalent cotransporter. Upon entry to the cell, iron encounters **mobilferrin** (aka "iron mobilizer"), which acts as a chaperone to the basal domain of the enterocyte. There it releases the iron at the basolateral transporter **ferroportin** (aka "iron portal"), which pumps the Fe^{2+} into the veins of the portal circulation. Fe^{2+} is oxidized to Fe^{3+} and immediately assembled onto the iron-transport protein **transferrin** (aka "iron transporter"). Transferrin is how iron circulates through the bloodstream. Transferrin receptors exist on all cells that require iron. Activation of transferrin receptors induces endocytosis, where the transferrin and iron are metabolized in endosomes. Free iron in the blood is bad.

How Iron Gets into the Blood

The initial absorption of iron by the duodenum (discussed above) is one way blood iron levels increase.

The other way is by the death of red blood cells. Whether old (the whole red blood cell is phagocytosed) or dying (free hemoglobin is phagocytosed), **macrophages** deal with excess hemoglobin. They break down the hemoglobin to heme and globin. The globin proteins are digested down to their constituent amino acids. The heme is separated into the porphyrin ring and the **iron**. The porphyrin ring is **unconjugated bilirubin**, which is sent, bound to albumin, to the liver for elimination. The iron has two choices. The first is to stay within the macrophage, which keeps it as **hemosiderin**. The second is to be released through a transport protein called **ferroportin**. Yes. The same transporter that is on the basal domain of the duodenal enterocyte is on the macrophage.

Hemosiderin is considered the "stored form" of iron within cells that don't want iron. Hemosiderin is toxic to most cells, so we want you thinking of hemosiderin not as "stored iron" but as "toxic waste iron." Macrophages have to deal with the most iron because they degrade hemoglobin. Other cells can have hemosiderin as well, a product of excess iron spilling into tissues that don't want it. Ferritin is the healthy iron stores that can be called upon when needed for more hemoglobin synthesis. Iron stores in the marrow and liver are ferritin. Hemosiderin is leftover iron that happens to be in cells.

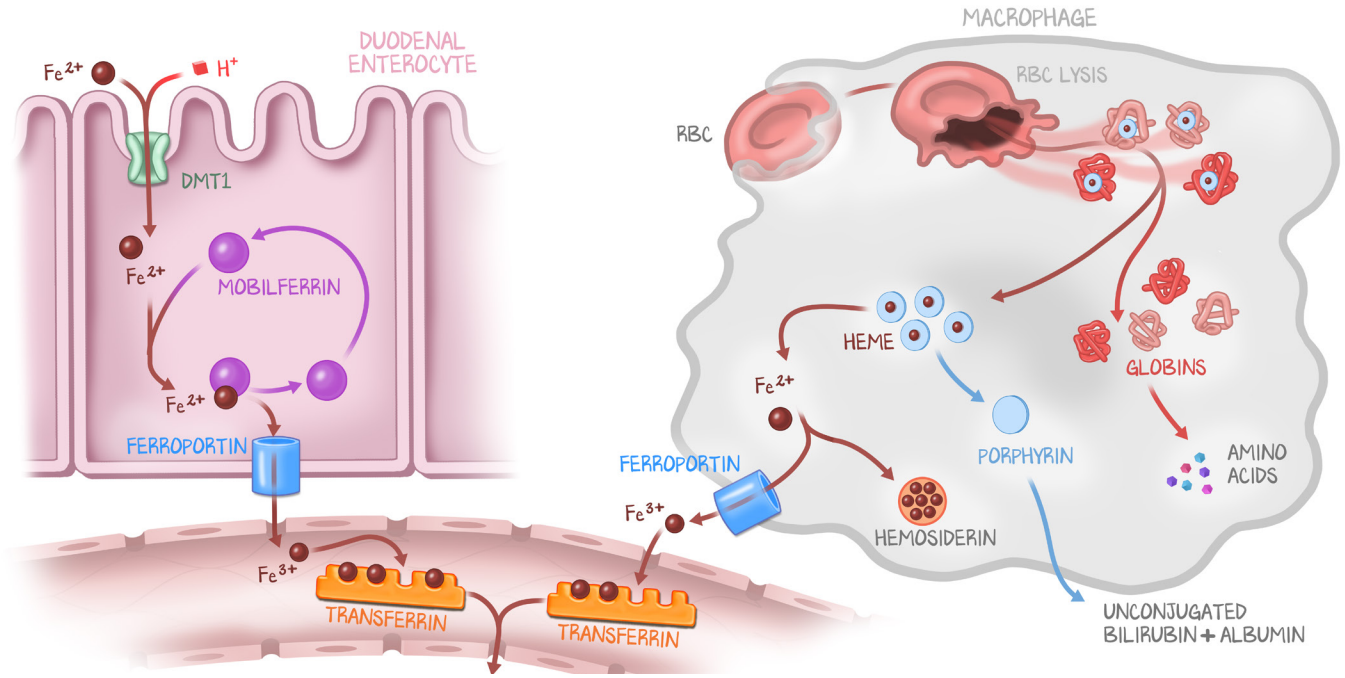

Figure 3.1: How Iron Gets into Cells and the Blood
From the diet, iron is absorbed from the lumen into the duodenal enterocyte by DMT1, transported to the basolateral membrane by mobilferrin, and released into the bloodstream by ferroportin. That iron is bound to transferrin for transfer to the liver through the portal circulation. Iron also comes from the hemolysis of red blood cells. Macrophages engulf red blood cells (or take up free hemoglobin) and break hemoglobin down into globins, porphyrin rings (released as bilirubin), and iron. Macrophages either keep iron as hemosiderin or release it onto transferrin.

Where Iron Goes

Iron is then dispatched throughout the body. Iron stores, the iron reserves, are in the stored form of iron called **ferritin**. Ferritin is located in the liver and bone marrow.

Red blood cells carry hemoglobin to best carry oxygen. Hemoglobin is formed from heme and globins. Heme is made of a porphyrin ring and **iron**. Transferrin brings iron to the bone marrow, where the iron-covered transferrin is endocytosed. The vesicle carrying iron-covered transferring fuses with the mitochondria, delivering transferrin and the iron directly to the site of heme synthesis.

All cells need iron to a small extent, and transferrin transfers iron from the gut or from ferritin iron stores to whatever cell needs it. But for the story of this lesson, we want you seeing iron-in-from-duodenum, iron-delivered-to-marrow-and-liver.

There are 4–5 grams of iron in a normal human. Two-thirds of that iron is dedicated to the synthesis of hemoglobin.

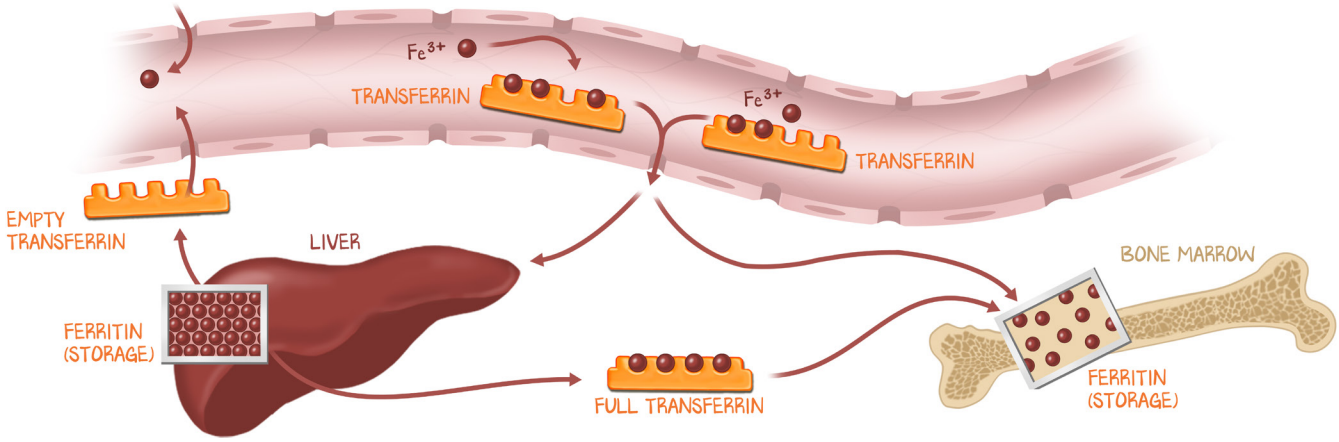

Figure 3.2: Where Iron Goes
Iron is added to transferrin. Transferrin takes iron to the cells of the body. Transferrin takes iron to the liver, where transferrin receptors endocytose and store iron as ferritin. The liver also makes transferrin. Transferrin also takes iron to the erythroblasts of the bone marrow, who endocytose iron-on-ferritin for use in hemoglobin synthesis. There is a small amount of ferritin in the marrow as well. Transferrin also brings iron to every other cell. Transferrin receptors induce endocytosis, and the iron is processed in the endosome.

Regulation of Iron

Women in their reproductive years are able to have menses. Men never have menses. Women who elect for hormonal or intrauterine contraception may have no menses. **Bleeding is the only way to meaningfully eliminate iron**. The only physiologic form of bleeding is menses. Iron is eliminated in bile, sweat, and other bodily secretions to a small extent, but the amount of iron lost that way is only a small fraction of what is ingested. Most of the iron we eat is NOT absorbed. It is true that iron is lost in feces. However, the iron lost in feces is the iron that enterocytes absorbed across the apical membrane but didn't release into the blood through ferroportin, and is not active secretion or elimination of blood iron. "Not absorbing" is not the same as "actively eliminating."

The only meaningful regulation of iron is to control the iron-in signal at the level of the **ferroportin channel**. Both duodenal enterocytes and macrophages possess a ferroportin channel. If the system demands more iron in the blood, these channels are open, and both macrophage and duodenal enterocyte are releasing iron into the bloodstream. If no iron is needed, the ferroportin channel is closed, and neither macrophage nor duodenal enterocyte releases iron. Macrophages store it as hemosiderin; enterocytes hold onto it until they slough off and die, being released through stool. This "loss of iron through the stool" is not a mechanism of elimination of iron from the blood; it is merely the voiding of iron that never got absorbed.

The only meaningful regulation is control over how much iron gets in via ferroportin. What regulates ferroportin is the liver, using the hormone hepcidin.

Hepcidin controls whether ferroportin is active or inactive. Hepcidin is synthesized by the **liver** (hepatocyte). The liver is also the main site of iron storage. Hepatocytes secrete hepcidin when stimulated by the **presence of iron** (having iron in hepatocytes increases hepcidin to decrease the amount of iron absorbed) or by the presence of **inflammation** (IL-6), possibly as part of a defense mechanism against bacteria. The human body is many cells working in concert. The constant supply of iron to the bone marrow ensures that red blood cells are being constantly made. But since red blood cells last 120 days, the human body doesn't need to maximize a constant supply of iron to the bone marrow. Bacteria, on the other hand, who utilize the nutrients circulating in the bloodstream to establish an infection, do not have the luxury of waiting it out the way our whole body does. So, during times of acute inflammation (which should be from acute infection), the liver silences iron movement into the blood by secreting hepcidin to inhibit ferroportin.

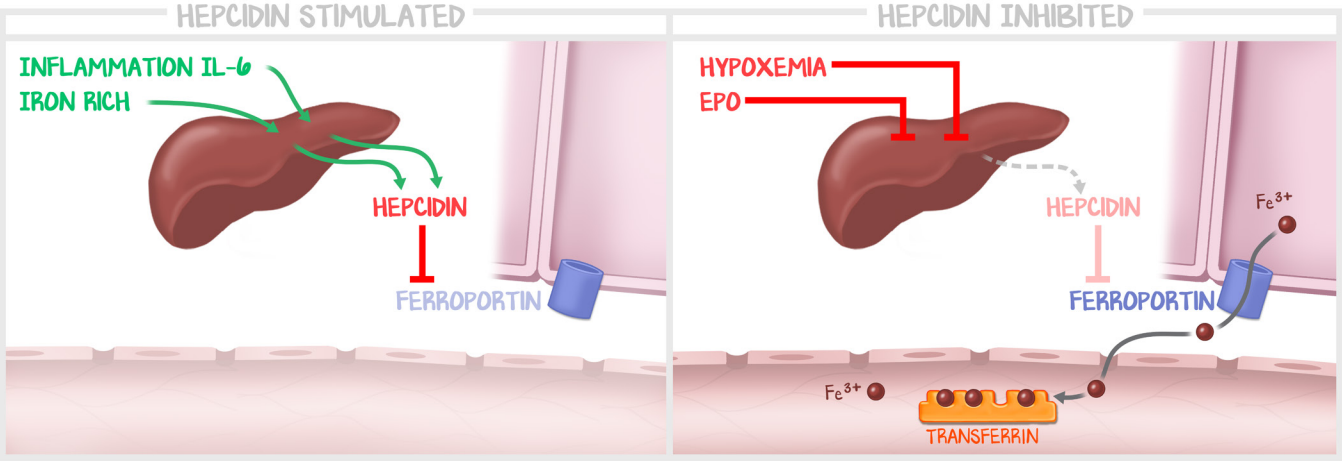

Figure 3.3: Regulation of Iron via the Liver
Hepcidin is released from the liver. Hepcidin inhibits ferroportin, inhibiting iron into the body and into the blood. Hepcidin is stimulated at times when iron is not needed (iron-rich states and inflammation) and inhibited at times when iron is needed (EPO stimulation).

The liver can listen to other organs' signals, as well. **Erythropoietin (EPO)** is secreted by the kidney when the kidney senses a low circulating oxygen. EPO tells the bone marrow to make more red blood cells. To make more red blood cells, the bone marrow will need to make more hemoglobin. To make more hemoglobin, the bone marrow will need more iron. EPO inhibits hepcidin release, disinhibiting ferroportin. Kidney hypoxia is communicated via EPO, which inhibits hepcidin. Hepatic hypoxia, though a weaker signal than the kidney's EPO, also inhibits hepcidin.

The Iron Silos and Iron Labs

Four values will come back when you order iron studies—transferrin/TIBC, percent saturation, ferritin, and serum iron.

Transferrin is how much protein there is that could bind to iron in the blood. It is quantified by the lab test **Total Iron-Binding Capacity** (TIBC). Each transferrin molecule has a number of open seats, seats that could be filled by iron. The **percent saturation** of transferrin is a product of how much transferrin there is (the TIBC, whether bound to iron or not) and how much iron there is. The more iron and the less transferrin, the higher the percent saturation. This is **NOT pulse oximetry** where "% sat" represents the amount of oxygen on each hemoglobin. The transferrin percent saturation is a marker for how much iron is circulating in the blood relative to how hard the liver is trying to deliver iron in the blood (the transferrin). We can also just simply measure the **serum iron** to know how much iron is circulating in the blood. Finally, the lab test that tells us what the iron stores are like is the **ferritin**. Using these four laboratories, we can assess a patient's iron status, as we will consciously do in the lesson on iron deficiency.

There is a complicated way to explain iron studies, and there is the OME way. For each of the different pathologic conditions, one could describe the system, the inhibition and stimulation, the cross-talk throughout the body. For example, when explaining iron deficiency anemia, you could do something like this: When iron is deficient, the body wants to be ready to pick up any iron that might come its way. To "be ready to pick up any iron" means transferrin will increase—the number of seats that could hold iron goes up. Therefore, while the transferrin rises, because there is no iron, the transferrin percent saturation falls. Because there is no iron, the serum iron is low. Because there is no iron in the stores, the ferritin is low.

Here at OME, we have a different way of looking at it. Ours is simpler, and gets you to where you need to be 90% of the time. The iron silos use a visual representation of a grain silo connected to a hose with a valve. The valve is ferroportin. Hepcidin closes the valve (by being active) or opens the valve (by being inhibited). The silo consists of stored iron (ferritin) and space left to fill with iron (the TIBC). The iron silo model assumes a steady input of iron, one that does not change, a steady dripping of iron into the silo. Therefore, the only thing that controls how much iron is in the blood or in the silo is the valve.

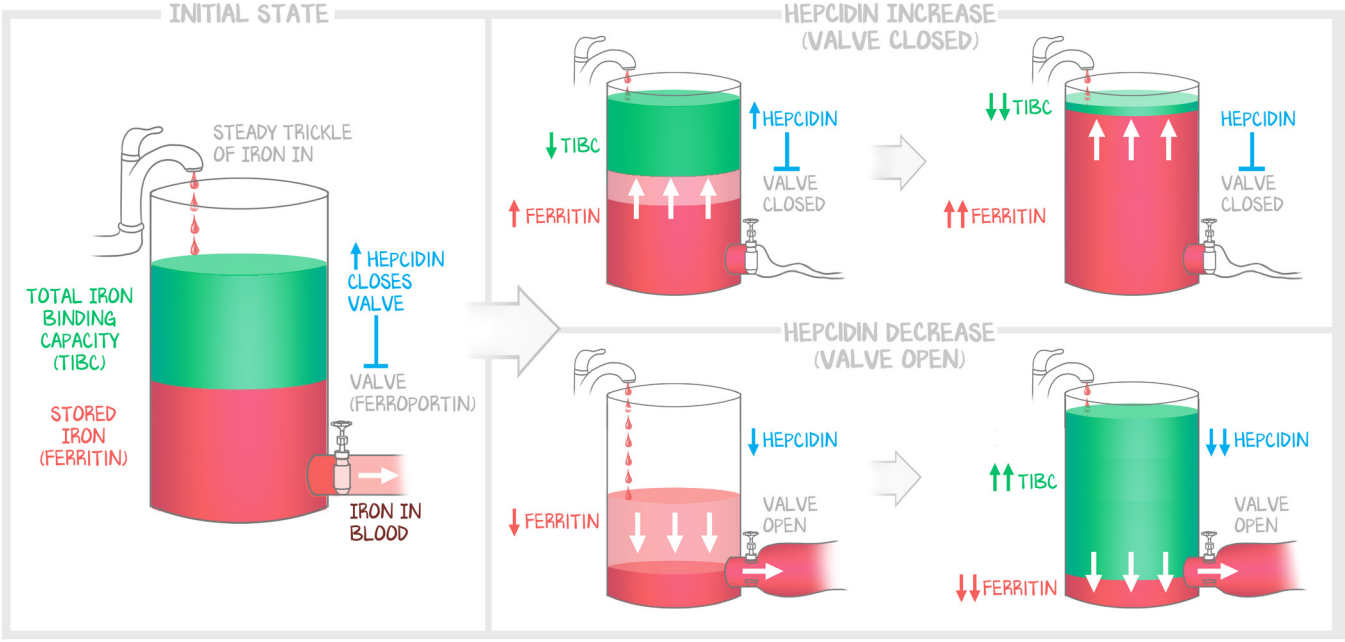

Figure 3.4: Working Through Iron Labs
Start at the left image, the initial state. In the top path, hepcidin is increased, and the valve is closed. If the valve is closed and the intake of iron continues at a continuous small rate, iron accumulates in the silos. This causes the ferritin to rise. If the ferritin goes up, and the silo is one size, there is less room for the TIBC/Transferrin, so the TIBC goes down. In the bottom path, the valve is fully opened, draining the iron from the silo. With more iron coming out and an unchanged amount coming in from the faucet, ferritin decreases. With less ferritin, there is more room for the TIBC.

With the iron silo method, you can more easily visualize what's happening. The faucet that fills the iron silos is always on. But it's always on just a little bit. This represents the very small percentage of ingested iron that gets absorbed through the ferroportin channel of duodenal enterocytes. The bone marrow uses whatever it needs from the iron stores. At the bottom of the iron silo is a valve. When more iron is needed by the marrow, the valve opens, draining the silo. When no more iron is needed by the marrow, the valve closes. The constant dripping into the silo eventually fills it up. All the iron in the silo is the stored form of iron, ferritin. The rest of the silo, the total amount of space left for iron, is the total iron-binding capacity. Now, one need determine only what the pathologic state will do—open the valve and drain the silo (ferritin down, TIBC up), or close the valve and fill the silo (ferritin up, TIBC down).